IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

THE PROCTER & GAMBLE COMPANY, Plaintiff, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	)	Civil Action No. 04-940 (JJF)

DEFENDANT TEVA PHARMACEUTICALS USA, INC.'S PROPOSED FINDINGS OF FACT

December 20, 2006

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I. BACKGROUND

1. Plaintiff Procter & Gamble Co. ("P&G") is an Ohio corporation having a principal place of business in Cincinnati, OH.

2. Defendant Teva Pharmaceuticals USA, Inc. ("Teva USA") is a Delaware corporation having a principal place of business in North Wales, PA.

3. P&G markets the pharmaceutical product Actonel for the treatment of diseases of bone metabolism, in particular osteoporosis and Paget's disease. Risedronate is the active ingredient in Actonel. The FDA approved Actonel as a 30 mg daily dose for the treatment of Paget's disease in 1998, and as a 5 mg daily dose and a 35 mg once-weekly dose for the treatment of osteoporosis in 2000 and 2002 respectively. (Joint Statement of Admitted Facts No. 15, D.I. 71.)

4. U.S. Patent 5,833,122 ("the '122 patent") issued December 10, 1996, and expires December 10, 2013. (JTX1.) The '122 patent is assigned to P&G, and P&G has listed the patent in the FDA's "Orange Book" as covering the various approved dosages and uses of Actonel.

5. Teva USA has filed an Abbreviated New Drug Application seeking approval to market generic equivalents of the Actonel 5 mg, 30 mg and 35 mg dosage forms before the expiration of the '122 patent. Teva USA submitted a certification to the FDA that the '122 patent is invalid, unenforceable or would not be infringed by the commercial manufacture, importation into the United States or sale or use within the United States of Teva USA's proposed commercial risedronate products. On July 2, 2004, Teva USA provided a notice of its certification to P&G in accordance with 21

U.S.C. § 355(j), and P&G brought suit for infringement of the '122 patent in this Court on August 13, 2004. (D.I. 1.)

II. THE '122 PATENT

6. P&G filed the application for the '122 patent on December 6, 1985, in the names of James J. Benedict and Christopher M. Perkins. (JTX1.) The application was a continuation-in-part of U.S. Application Ser. No. 684,543 ("the '543 application"), filed December 21, 1984. P&G has stipulated that the '543 application does not support any of the asserted claims of the '122 patent. (D.I. 86.)

7. The '122 patent relates to a particular class of bisphosphonates for use in treating diseases associated with abnormal calcium and phosphate metabolism. The patent refers to a wide variety of diseases including osteoporosis, Paget's disease and hypercalcemia of malignancy. (JTX1, col.1, ll.26-53.)

8. The '122 patent includes 23 claims. P&G has asserted claims 4, 16 and 23. Claim 4 recites a chemical compound:

> A disphosphonic acid compound, or pharmaceutically acceptable salt or ester thereof, which is 2-(3-pyridyl)-1-hydroxyethane diphosphonic acid.

Claim 16 recites a pharmaceutical composition. Written in independent form, it states:

> A pharmaceutical composition comprising
>
> (a) a geminal diphosphonic acid compound or a pharmaceutically acceptable salt or ester thereof, at a level providing from 0.001 to 600 milligrams of phosphorus in said composition, wherein said diphosphonic acid compound is 2-(3-pyridyl)-1-hydroxyethane diphosphonic acid; and
>
> (b) a pharmaceutically acceptable carrier.

Claim 23 defines a method of treatment:

> A method of treating diseases associated with abnormal calcium and phosphate metabolism, comprising administering to a person in need thereof a safe and effective amount of a composition of claim 16.

(JTX1; DTX309, 311 and 312.)

9. The chemical compound recited in all three asserted claims has the generic name "risedronate." It was referred to internally at P&G as "3-pyr EHDP," and by its compound number "NE-58019." (DTX307; Lenz 93.)

III. BISPHOSPHONATES FOR THE TREATMENT OF BONE DISEASES

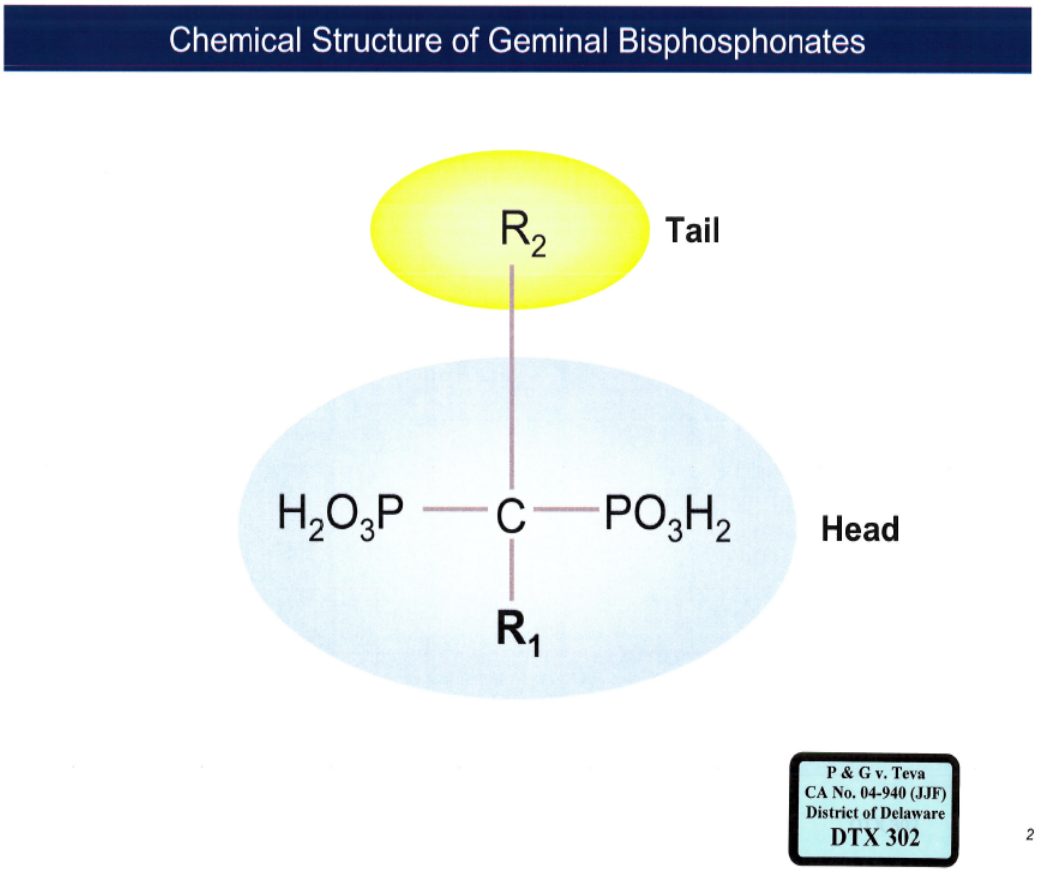
10. By mid-1985, it was known that bone continuously regenerates itself by a process in which old bone is removed and replaced by new bone. This process is called bone remodeling. The old bone is removed by cells called osteoclasts and replaced by cells called osteoblasts. When the balance between bone destruction and bone formation is disrupted, bone disease results. For example, in osteoporosis, more bone is destroyed than is replaced, which results in loss of bone. (Bilezikian 352-56; Lenz 84-85.)

11. By mid-1985, bisphosphonates, also called "diphosphonates," as a class were known to inhibit bone resorption, and therefore to have utility in the treatment of bone diseases. (Lenz 68, 85-86; Bilezikian 403, 408.)

12. Bisphosphonate molecules include two phosphonic acid groups. In "geminal" bisphosphonate compounds the phosphonic acid groups are attached to a central, "geminal," carbon atom. The geminal carbon atom also has two additional groups attached to it. In chemical nomenclature, those groups are known as substituents and are typically labeled R_1 and R_2. (Lenz 69-70; DTX302.)

13. From the viewpoint of a medicinal chemist, bisphosphonates have two parts, a "head" and a "tail." The head portion contains the geminal bisphosphonate group

(the central carbon atoms and the phosphonic acid groups) and the R_1 substituent. The tail includes the R_2 substituent. The chemical structure of geminal bisphosphonates showing the head and tail is shown below. (Lenz 71-72.)



14. The head accounts for the affinity of the molecule for bone. Typically R_1 is a hydroxy (–OH) group. By 1985, persons skilled in the art understood that the head should include the hydroxy function. (Lenz 70-71; McKenna 647-48; Bilezikian 408.)

15. The tail, or the R_2 group, is the portion that the medicinal chemist would vary in order to make new compounds. (Lenz 72.)

16. By mid-1985, the mechanism by which bisphosphonates inhibited bone resorption was not well understood, although it was known that the mechanism included

interference with osteoclast function. This "knowledge gap," however, was not a deterrent to research in this area because established biological assays existed to test for the desired activities. Thus in-depth knowledge of the mechanism of action was not necessary. In fact, at the time there were many therapeutic areas in which the mechanism of action was not understood on a molecular level, but biological assays to test for the desired activity were available. (Lenz 85-87.)

17. At that time, it was also known that bisphosphonates could interfere with the mineralization process which occurs during the bone formation phase of the bone remodeling process. This activity was known to be undesirable in particular for compounds destined for the treatment of osteoporosis. Researchers were therefore looking for compounds that inhibited bone resorption without interfering with bone mineralization. (Lenz 80-81.)

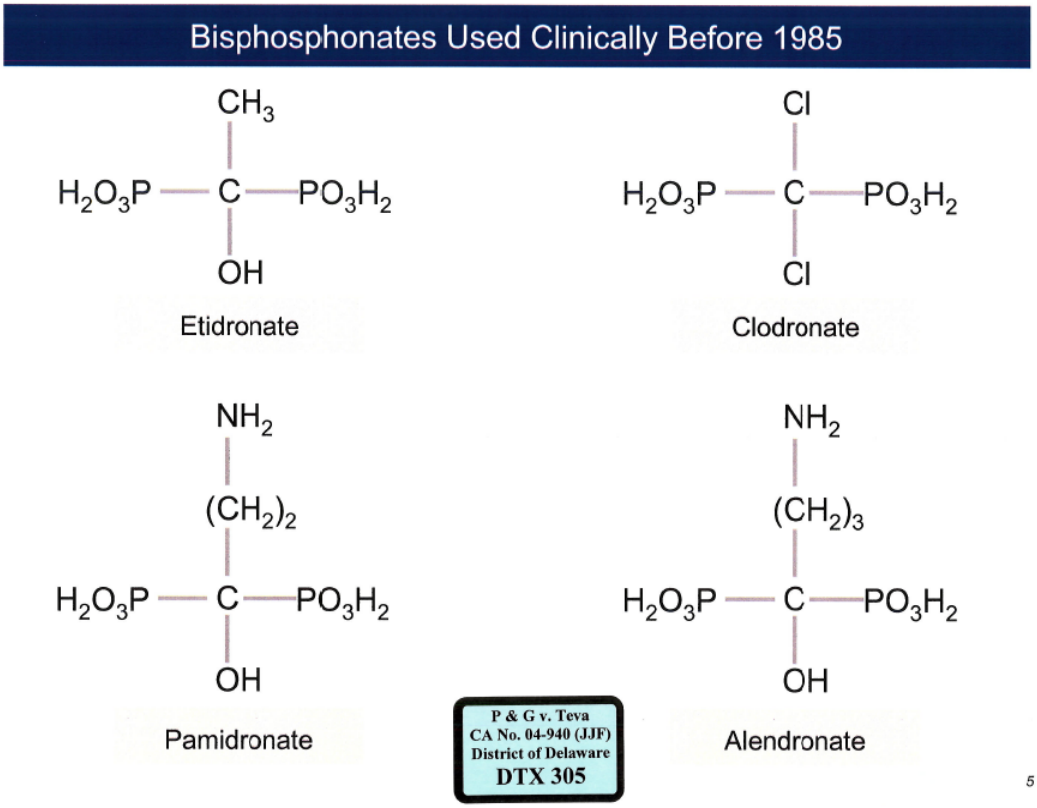
18. Biological assays were available in the mid-1980's to test for compounds that inhibited bone resorption without interfering with bone mineralization. (Bilezikian 404.)

19. Scientists first began studying bisphosphonates for the treatment of bone diseases in the 1960's and 70's. The first compound that came out of this research was known as etidronate, which was clinically tested and ultimately approved for the treatment of Paget's disease. It is still marketed today. (Lenz 79-80; Bilezikian 377.)

20. The chemical name of etidronate is 1-hydroxy-ethane-1,1-disphosphonic acid or EHDP for short. Etidronate is a geminal bisphosphonate in which R_1 is a hydroxy group and R_2 is a methyl ($-CH_3$) group. (DTX304; Lenz 80.)

21. Although etidronate exhibited significant inhibition of bone resorption, it also inhibited bone mineralization to an undesirable degree, so that the drug was not ideal for the treatment of osteoporosis. Researchers therefore continued to search for additional bisphosphonates that had a profile better suited to the treatment of osteoporosis. (Lenz 80-81; Bilezikian 377.)

22. By mid-1985, at least three other bisphosphonates were being evaluated clinically for the treatment of osteoporosis: pamidronate, clodronate and alendronate. Alendronate and pamidronate differ from etidronate and each other only in the composition of the R_2 group. Clodronate differs from all these compounds in that both R groups are chlorine atoms. (Lenz 81-83.) The chemical structures for etidronate, pamidronate, clodronate and alendronate are shown below.

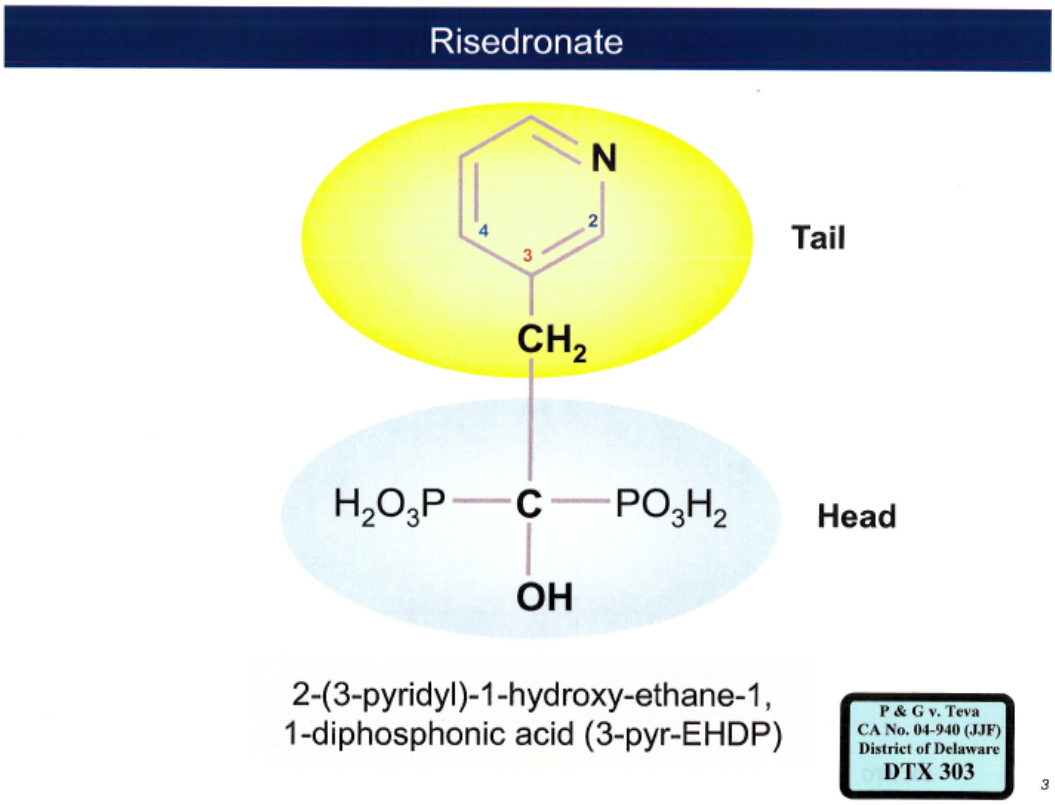


23. Etidronate, pamidronate and alendronate are all marketed in the United States for the treatment of bone disease. Although clodronate has not been approved for sale in the United States, it is being marketed in Europe for the treatment of bone disease. (Lenz 82.)

24. Both alendronate and pamidronate include nitrogen in their R_2 groups. Both compounds were known to be potent bone inhibitors of bone resorption having a low potential for inhibiting bone mineralization. In fact, by mid-1985, nitrogen-containing bisphosphonates in general were known to have a much more pronounced effect on bone resorption in comparison to bone mineralization. Alendronate in particular was found to have an excellent inhibition of bone resorption to inhibition of bone mineralization ratio. It was known that alendronate was 100 times as effective as pamidronate. (DTX42, col.13, ll.35 – col.14, ll.13.)

IV. RISEDRONATE AND 2-PYR EHDP

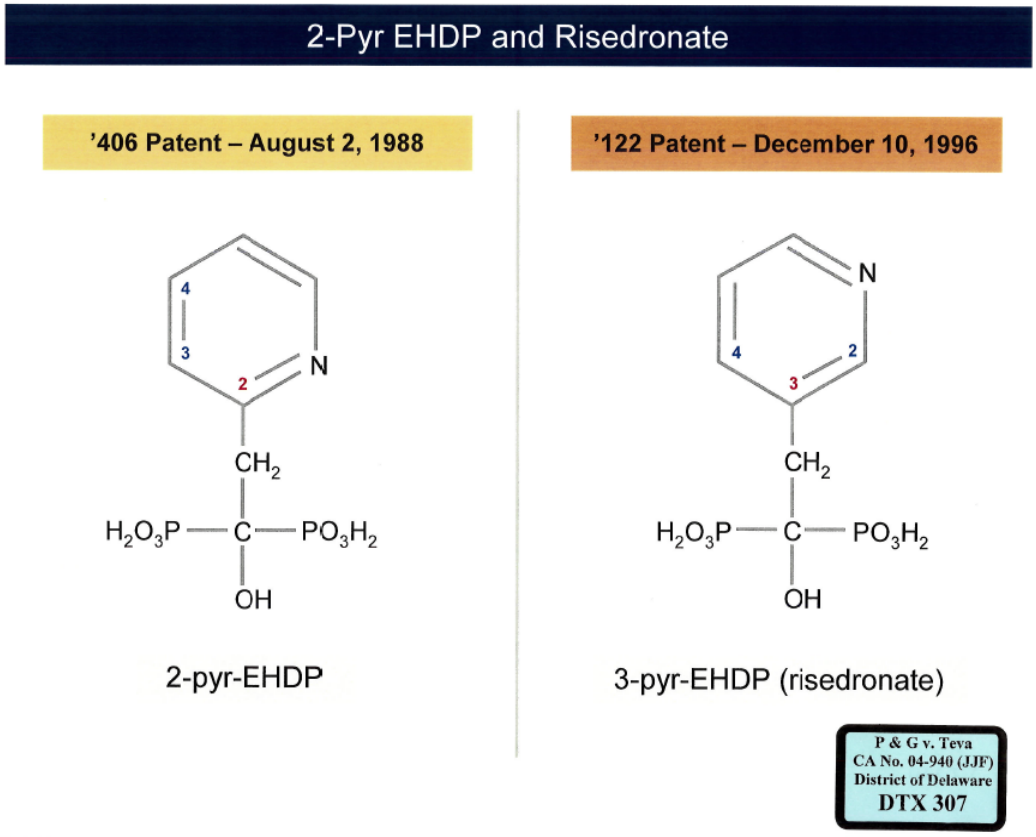
25. The risedronate molecule, like the prior bisphosphonates, has a head and a tail. In risedronate, the head is identical to that of etidronate, pamidronate and alendronate, and the R_1 group is hydroxy. The tail, however, consists of a "pyridine" ring, which a six-membered ring consisting of five carbon atoms and one nitrogen atom. The risedronate molecule is depicted below:



26. Although P&G has asserted only claims that are specific to risedronate, other claims of the '122 patent are not restricted to that compound. In particular, the patent also includes claims to a closely related compound, 2-pyr EHDP (also referred to as 2-(2-pyridyl) hydroxyethane-1,1-diphosphonic acid). That compound is covered generically by claims 2 and 3. Pharmaceutical compositions of that compound are covered by claims 12 and 14, and the use of that compound to treat diseases associated with abnormal calcium and phosphate metabolism is covered by claim 21. (JTX1.)

27. Risedronate and 2-pyr EHDP are isomers. The only difference between the risedronate molecule and that of 2-pyr EHDP is the point of attachment of the pyridyl group to the linking carbon. In 2-pyr EHDP the linking carbon is attached to the pyridyl

group at the 2-position. This is why it is known as 2-pyr EHDP, whereas risedronate, in which the pyridyl group is attached to the linking carbon at the 3 position, is known as 3-pyr EHDP. The number identifies the point at which the EHDP portion of the compound is substituted onto the pyridine ring. The chemical structures of risedronate and 2-pyr EHDP are shown below.



28. Another way of referring to the difference between the two molecules is to refer to the position of the nitrogen on the pyridine ring. Risedronate and 2-pyr EHDP are positional isomers. They have the same atomic composition and the same molecular weight, and differ from each other only in the position of the nitrogen atom in the pyridine ring. (Lenz 92.)

V. PROSECUTION OF THE ASSERTED CLAIMS OF THE '122 PATENT

29. Although P&G filed the application for the '122 patent in late 1985, that application did not include any claims specific to risedronate, pharmaceutical compositions containing risedronate, or the use of risedronate for treatment of disease. P&G did not present a claim to the compound risedronate (as claimed in asserted claim 4), in Application Ser. No. 806,155 ("the '122 patent application") until October 24, 1995, nearly 10 years after filing the application. (JTX2 at 208.)

30. In addition, P&G did not present either a claim to a pharmaceutical composition containing risedronate (application claims 70 and 72) (as claimed in claim 16), or a claim to a method of treatment using a pharmaceutical composition containing risedronate (application claims 81 and 83) (as claimed in claim 23) in the '122 patent application until July 22, 1988, more than three and a half years after filing the application. (JTX2 at 89, 91.)

31. After P&G had finally presented a claim to a pharmaceutical composition containing risedronate, on October 21, 1988, the examiner of the '122 patent application stated that the claim (application claim 70) would be allowable if placed in independent form. (JTX2 at 112.)

32. However, P&G did not accept the claim to a pharmaceutical composition containing risedronate. Instead, on March 24, 1989, P&G canceled it and replaced it with another claim (application claim 108). (JTX2 at 125.)

33. In the same amendment in which P&G rejected the examiner's invitation accept a claim to a pharmaceutical composition containing risedronate, P&G attempted to

provoke an interference with U.S. Patent 4,761,767 ("Bosies"), which claimed a series of bisphosphonates that did not include risedronate. (JTX2 at 134.)

34. The PTO declared an interference between certain claims of P&G's application and claims of the Bosies patent. None of the counts of the interference covered risedronate, pharmaceutical compositions containing risedronate, or a method of using risedronate. (JTX2 at 171.)

35. In the interference, P&G contended that the new claim to the risedronate composition (application claim 108) did not correspond to the count. (JTX2 at 134.)

36. P&G also eventually convinced the PTO to designate the claim to the risedronate composition as not corresponding to the interference count. (JTX2 at 152, 192-99.) As a result, that claim could not have been rejected over Bosies, and could have been issued in a patent even while the interference was pending. *See* 37 C.F.R. § 1.615 (1995); Manual of Patent Examining Procedure § 2315.01 (5th ed. 1983-1994).

37. Despite its success in removing the claims to the risedronate composition from the interference, P&G never prosecuted that claim during the five years that the interference lasted, even though it could have done so.

38. P&G ultimately lost the interference. (JTX2 at 200-03); *Bosies v. Benedict*, 27 F.3d 539 (Fed. Cir. 1995). However, because the risedronate claims of the application did not correspond to the count of the interference, the PTO allowed these claims over the Bosies patent and the count of the interference. (JTX2 at 112.)

39. Had P&G exercised its right to prosecute claims to risedronate while the interference was pending, those claims would probably have issued long before the '122 patent actually issued, and would expire long before the '122 patent will actually expire.

40. While the interference was pending, the risedronate compound had not yet received approval from the FDA. Therefore, P&G had no immediate impetus to pursue patent claims covering risedronate. The patent term did not begin to run until the patent issued, and if the patent issued later a shorter portion of its term would run while P&G awaited FDA approval. Thus, more of the patent term would remain to protect the drug after it entered the market.

VI. THE '406 PATENT

41. U.S. Patent 4,761,406 is assigned to P&G. It issued August 2, 1988, and expired August 2, 2005. It lists Lawrence Flora and Benjamin Floyd as the inventors. Those inventors filed the application which led to the '406 patent, U.S. Application Serial No. 741,976, on June 6, 1985, six months before Drs. Benedict and Perkins filed the application for the '122 patent. (JTX5.)

42. The '406 patent includes claims directed to the treatment of osteoporosis by the administration of several bisphosphonate compounds, including 2-pyr EHDP. (JTX5, claim 15.)

43. Although the '122 patent claims 2-pyr EHDP, compositions containing 2-pyr EHDP, and the use of 2-pyr EHDP, the '122 patent application did not reference the application for the '406 patent, which was filed before the '122 patent application and named a different inventive entity. (JTX2.)

44. P&G never brought the application for the '406 patent or the '406 patent itself to the attention of any of the examiners of the application for the '122 patent during the latter application's eleven-year pendency in the PTO. (JTX2.)

45. Claim 15 of the ’406 patent discloses a method of treating osteoporosis using a dosing regimen in which one of several bisphosphonates (including 2-pyr EHDP) is administered to the patient on a cyclical basis, meaning that treatment periods during which the drug is administered are alternated with rest periods during which no drug is administered. Claim 15 states:

> **15.** A method according to claim 1 wherein the bone resorption inhibiting polyphosphonates, and daily dosage ranges, are selected from the group consisting of:
>
> Ethane-1-hydroxy-1,1-diphosphonic acid: from about 0.25 mg P/kg to about 4 mg P/kg;
>
> Dichloromethane diphosphonic acid: from about 0.12 mg P/kg to about 5 mg P/kg;
>
> Propane-3-amino-1-hydroxy-1,1-diphosphonic acid: from about 0.025 mg P/kg to about 1 mg P/kg;
>
> Butane-4-amino-1-hydroxy-1,1-diphosphonic acid: from about 0.0025 mg P/kg to about 0.1 mg P/kg;
>
> Hexane-6-amino-1-hydroxy-1,1-diphosphonic acid: from about 0.025 mg P/kg to about 1 mg P/kg;
>
> 2-(2-pyridyl-ethane-1,1-diphosphonic acid: from about 0.0025 mg P/kg to about 0.1 mg P/kg;
>
> **[2-pyr EHDP]: from about 0.00025 mg P/kg to about 0.01 mg P/kg; and/or**
>
> Hexahydroindan-2,2-diphosphonic acid: from about 0.25 mg P/kg to about 10 mg P/kg;
>
> and their pharmaceutically-acceptable salts and esters.

(JTX5; emphasis added.)

46. Claim 15 depends from claim 1, which reads:

> **1.** A method for treating osteoporosis, in humans or lower animals afflicted with or at risk to osteoporosis, comprising administering to said human or lower animal an effective amount of a bone resorption inhibiting polyphosphonate according to the following schedule:
>
> (a) a period of from about 1 day to about 90 days during which said bone resorption inhibiting polyphosphonate is administered daily in a limited amount; followed by
> (b) a rest period of from about 50 days to about 120 days; and
> (c) repeating (a) and (b) two or more times where a net increase in bone mass said human or animal results.

(JTX5.)

47. The ranges in claim 15 are in units of mg P/kg, which means that the amount of drug administered will be adjusted relative to the weight of the human or animal being treated.

48. The language "*a* bone resorption inhibiting polyphosphonate" indicates that the method is to be used with any *one* of the bisphosphonates listed in claim 15, making that claim cover eight discrete embodiments, one for each compound listed. One of those bisphosphonates is 2-pyr EHDP.

49. Claim 15 lists the dosing ranges in mg of phosphorous per kilogram of body weight for each of the listed bisphosphonates. According to claim 15, 2-pyridyl EHDP is to be dosed at the lowest dose of all the listed compounds. This indicates that 2-pyr EHDP is the most potent compound in the group. (McKenna 683-84; Lenz 88-90.)

VII. THE CLAIMED INVENTIONS OF THE '122 PATENT WOULD HAVE BEEN OBVIOUS IN VIEW OF THE CLAIMED INVENTION OF CLAIM 15 OF THE '406 PATENT

A. The Level of Ordinary Skill in the Art

50. The '122 patent is directed primarily to chemical compositions that could be used to treat diseases of bone metabolism, such as osteoporosis and Paget's disease. (Lenz 68, 74.)

51. The relevant art for the '122 patent is the art of medicinal chemistry and drug discovery. In the mid-1980s, a person skilled in the art had a Ph.D. in organic chemistry, and several years experience in the field. (Lenz 77-78.) Persons skilled in the art would also have experience working with heterocyclic compounds, of which pyridine is an example. (Lenz 73.) Such persons would also have experience in interpreting biological activity and toxicity data for compounds with which they were involved. (Lenz 59, 78-79.)

52. Dr. George Lenz, Teva USA's expert witness, has a Ph.D. degree in organic chemistry from the University of Chicago, which he obtained in 1967. He did post-doctoral research work at Yale University from 1967 to 1969. He worked in drug discovery for most of his professional career. (DTX134.) In the mid-1980s, Dr. Lenz was working in drug discovery at G.D. Searle, and had been working in the field for 15 years. His experience included a variety of therapeutic areas, including cardiovascular disease, gastrointestinal disease, and central nervous system diseases. (Lenz 57-58.)

53. The person of ordinary skill would not have required special training in organophosphorus chemistry. By 1985, organophosphorus chemistry was a well-developed field, and the synthesis of geminal bisphosphonate compounds was disclosed

in the technical literature. The chemistry of the compounds was well understood, and such compounds were straightforward to make. A simple, "one-pot" synthesis for such compounds was described in the literature, and the starting materials could be purchased from chemical suppliers. (DTX76; Lenz 109-111, Benedict 512.) When Dr. Benedict first made risedronate, he employed that procedure. (DTX150 at PG45560.)

54. Persons skilled in the art beginning an investigation of a therapeutic class of drugs often were not working with those drugs before they started. They typically educated themselves about the drugs by reading the technical literature. (Lenz 58-59.) For example, Dr. Lenz carried out a project involving new synthetic routes to certain steroid drugs, and was successful even though he had not previously worked with that class of compounds. (Lenz 53-56.)

55. Unlike Dr. Lenz, who had 15 years of drug discovery experience as of the mid-1980's, Dr. McKenna, P&G's chemistry expert, was not involved in drug discovery of any kind at that time. Specifically, in the mid-1980s he was not working on discovering new drugs for treatment of bone disease, nor was he making new bisphosphonates for any pharmaceutical purpose. His publication list does not include any papers on new chemical compounds for pharmaceutical use prior to 1985. (McKenna 639-46.)

B. Differences Between the Claimed Invention of the '122 Patent and the Claimed Invention of the '406 Patent

56. The claims at issue are claims 4, 16 and 23 of the '122 patent. The reference patent claim for obviousness-type double patenting is claim 15 of the '406 patent.

57. Claim 4 of the ’122 patent is a compound claim specific to risedronate. Claim 15 of the ’406 patent claims a method of administering several bisphosphonates, including 2-pyr EHDP. The only difference between risedronate and 2-pyr EHDP is the position of the nitrogen on the pyridine ring. (DTX309.)

58. Claim 16 of the ’122 patent claims a pharmaceutical composition containing risedronate in an amount from 0.001 to 600 mg of phosphorous and a pharmaceutically acceptable carrier. Claim 15 of the ’406 patent claims the administration of 2-pyr EHDP for the treatment of osteoporosis. One of ordinary skill in the art would understand that the administration would be accomplished using a pharmaceutical composition. (Lenz 113-14.) Furthermore, the dosage range in Claim 15 of the ’406 patent falls within the dosage range required by claim 16 of the ’122 patent. (Lenz 114-15.) Thus, the only element of claim 16 of the ’122 patent that is not within claim 15 of the ’406 patent is the substitution of risedronate for 2-pyr EHDP. The only difference between risedronate and 2-pyr EHDP is the position of the nitrogen on the pyridine ring. (DTX311.)

59. Claim 23 of the ’122 patent claims a method of treating diseases associated with abnormal calcium and phosphate metabolism by administering to a person in need thereof an effective amount of the composition of claim 16. Claim 15 of the ’406 patent claims a method of treating osteoporosis, which is a disease associated with abnormal calcium metabolism. (Lenz 116-17.) Thus the only element of claim 23 of the ’122 patent that is not within claim 15 of the ’406 patent is the substitution of risedronate for 2-pyr EHDP. The only difference between risedronate and 2-pyr EHDP is the position of the nitrogen on the pyridine ring. (DTX312.)

60. The only difference between claims 4, 16 and 23 of the ’122 patent and the prior art is the substitution of risedronate for 2-pyr EHDP and the only difference between those two molecules is the position of the nitrogen on the pyridine ring.

61. 2-pyr EHDP and risedronate have the same number of carbon, nitrogen, oxygen and hydrogen atoms. They have the same molecular weight. (DTX307; Lenz 92-3; McKenna 659-60.)

62. 2-pyr EHDP and risedronate are not “chiral” compounds; neither exists in the form of enantiomers, and they are not enantiomers of each other. (McKenna 674; Lenz 280-82.)

63. Both 2-pyr EHDP and risedronate exist as crystalline solids at room temperature. (McKenna 660; JTX1, col.8, ll.34-35.)

C. Persons Skilled in the Art Would Have Been Motivated to Make Risedronate in View of the Claimed Invention of Claim 15 of the ’406 Patent

64. A person of ordinary skill in the art who was aware of claim 15 of the ’406 patent would have been motivated to move the position of the pyridine ring on 2-pyr EHDP to make risedronate.

65. Based on claim 15 of the ’406 patent a person of ordinary skill in the art would have understood 2-pyr EHDP to be safe and effective for the treatment of osteoporosis, a bone disease. That person would also have understood 2-pyr EHDP to be more potent than any of the prior art compounds, which were listed in the claim together with their preferred dosage ranges. (Lenz 90.)

66. That persons skilled in the art of medicinal chemistry were motivated to make all three positional isomers of pyridine-containing compounds is demonstrated by

the fact that those who actually discovered commercial drug substances often did so. In particular, prior to 1980 the developers of the following drugs, all but one of which were commercial products, referred to all three possible pyridyl positional isomers of pyridine-containing compounds, and disclosed the conception, making and/or testing of two or more positional isomers:

Drug	Patent or Literature Reference	DTX	No. Isomers Disclosed or Tested
Milrinone	USP 4,004,012	45	All three (DTX45, col.2, ll.39-61; col.9, l.49 – col.11, l.14.)
Amrinone	USP 4,072,746	43	All three (DTX43, col.18, ll.64 – col.19, l.61.)
Zimelidine	USP 3,928,369	46	All three (DTX46, col.9, l.1; col.11, l.60.)
Propiram	USP 3,163,654	49	All three (DTX49, col .6, claims 3,5, & 6.)
Diisopyramid	USP 3,225,054	48	All three (DTX48, col.4, l.23 – col.5, l.6.)
Pinacidil	USP 4,057,636	44	Two (DTX44, col.5, l.9-22; col.9, ll.2–9.)
Piroxicam	USP 3,591,584	47	All three (DTX47, col.32, claim 12.)
Aza-Fentanyl	Analogs Arch. Pharm. 311:1010 (1979)	52	All three (DTX52, pp.1011-13.)

(DTX310; Lenz 98-105.)

67. In addition, Dr. Benedict himself followed this very methodology. He first synthesized 2-pyr EHDP by a difficult synthetic method. Then he found a "one-pot" synthesis in the patent literature, and immediately synthesized all three isomers by using readily available starting compounds. (DTX150 at PG45560; Lenz 111; Benedict 452, 511-12; McKenna 678-79.)

68. In 1985, while performing his own research in the pharmaceutical industry, Dr. Lenz purchased the same three pyridyl starting materials Dr. Benedict used to make each of the three isomers of risedronate. Dr. Lenz used those starting materials to make a series of pharmaceutical compounds that included each of the three pyridyl isomers, because he was motivated to study the properties of each. (Lenz 111-12.)

69. By December 6, 1985, there was ample literature that one of ordinary skill in the art could refer to for guidance on how to synthesize 2-pyr EHDP and its positional isomers. For example a synthesis for making aminobisphosphonates was disclosed in UK Patent Application No. 2 118 042 A, which covered alendronate. (DTX76.) This synthesis could be adapted to make 2-pyr EHDP and its positional isomers by changing the starting materials used to attach the R_2 group to the bisphosphonate head. In particular, instead of using aminobutyric acid, one of ordinary skill in the art could use 2-pyridyl acetic acid, 3-pyridyl acetic acid or 4-pyridyl acetic acid, depending upon which isomer was being synthesized. This is the same synthesis that was disclosed in the '122 patent for making 2-pyr EHDP. (JTX1, col.8, ll.17-36.) The starting materials for making each of the isomers were commercially available from the Aldrich catalogue at the time. (Lenz 111-12.)

D. The Person Skilled in the Art Would Have Had a Reasonable Expectation of Success

70. A person of ordinary skill in the art would have a reasonable expectation that risedronate and 2-pyr EHDP would have similar biological activities and could both be used in the treatment of diseases associated with abnormal calcium and phosphate metabolism, *i.e.*, bone disorders. (Lenz 96-97, 118-19.)

71. The two compounds are both bisphosphonates, which as a class were known at the time the invention was made to inhibit bone resorption to some degree. (Lenz 107-108; PTX355 at PG191240-41.)

72. The two compounds are also hydroxybisphosphonates which were known at the time the invention was made to have enhanced potency. (McKenna 669; Lenz 71; PTX355 at PG191241.)

73. The two compounds also belong to the class of nitrogen-containing bisphosphonates, which were known to have a much more pronounced effect on bone resorption in comparison to bone mineralization. (McKenna 670.)

74. The two compounds are positional isomers and only differ from each other in the position of the nitrogen on the pyridine ring. A person of ordinary skill would expect these compounds to have similar activities. (Lenz 92-93, 104-07.)

75. Dr. Benedict testified that two bisphosphonate compounds which were structurally similar would be expected to have similar biological activity. As an example of the type of difference that would have caused him to believe that the two compounds would have similar biological activity, Dr. Benedict identified the difference between a "two rather than a three substitution on a ring or something such as that." (Benedict 498.) This is precisely the difference between 2-pyr EHDP and risedronate.

76. In the mid-1980s, persons skilled in the art knew that bisphosphonates as a class of compounds inhibited bone resorption. In addition, persons skilled in the art were aware that the addition of the hydroxy (–OH) group to the head of the bisphosphonate molecule would enhance bone resorption inhibition activity. (PTX355 at PG191240-41; McKenna 667, 670-71; Lenz 71, 107-108.)

77. In the mid-1980s, persons skilled in the art were aware that adding a nitrogen-containing substituent to the bisphosphonate tended to enhance bone resorption inhibition activity. (Lenz 71, 107-108; McKenna 667, 669-71.)

78. 2-pyr EHDP is a bisphosphonate, it has a hydroxy group incorporated into the head portion of the molecule, and it has a nitrogen-containing substituent on the tail portion of the molecule. (Lenz 91-93; McKenna 658-60.)

79. Risedronate is a bisphosphonate, it has a hydroxy group incorporated into the head portion of the molecule, and it has a nitrogen-containing substituent on the tail portion of the molecule. (Lenz 74-75; McKenna 658-60.)

80. Because of the close structural similarity between 2-pyr EHDP and risedronate, and because risedronate is a bisphosphonate, includes a hydroxy group in the head portion, and a nitrogen-containing substituent on the tail portion, a person skilled in the art who was aware of the activity of 2-pyr EHDP would have reasonably expected risedronate likewise to have bone resorption inhibition activity. (Lenz 92-93, 104-107.)

81. A person skilled in the art who was aware of the potent bone resorption inhibition activity of 2-pyr EHDP would have been motivated to make the other two positional isomers (risedronate and 4-pyr EHDP). This motivation would have arisen both because of a belief that risedronate would have similar activity and in order to study the structure-activity relationship among the three isomers. (Lenz 96-98.)

E. Risedronate Does Not Exhibit Any Unexpected Results Compared to 2-pyr EHDP

1. P&G's Activity Testing Shows that Risedronate Does Not Exhibit Any Unexpected Potency Advantage Over 2-pyr EHDP

82. During the mid-1980s, P&G employed two animal tests to screen compounds for inhibition of bone resorption activity: the TPTX test and the Schenk test. (Miller 840-41.)

83. In the TPTX test, the test animals (rats) are treated surgically to remove their thyroid and parathyroid glands. The latter gland secretes a hormone that regulates calcium metabolism, including bone resorption. The rats are then fed a low calcium diet. (Miller 845-47.) After the calcium blood level has become minimized, the animals are administered the test drug for several days, followed by a dose of parathyroid hormone. The hormone stimulates bone resorption, increasing the blood calcium level. The blood calcium level is measured, and if the test compound is active to inhibit bone resorption, the level will be lower than for the control. (P038.) For many compounds, P&G carried out this test on several different groups of rats, each one receiving a different dose. The lowest dose at which activity was observed was called the "lowest effective dose," or "LED" for the compound. (Lenz 131-32.)

84. In addition to the TPTX test, P&G employed the Schenk test. In this method, young growing rats are injected with a compound that "marks" the bones so that the experimenter later examining the bones can determine the beginning of the experiment. (Lenz 132-33.) The rats are administered the test compound for several (typically seven) consecutive days. (Miller 849.) One group of rats are not administered

the test compound, and acts as a control group. At the end of the test period, the animals are killed and the tibiae are dissected and observed.

85. At P&G, the earlier analyses of the tibiae were performed by a histological method; that is, the dissected bone was examined microscopically and the percent trabecular bone was determined. The percent trabecular bone in the control group was subtracted from that number. The greater this difference, the more active the test compound was at inhibiting bone resorption. (McOsker 716-17.) As with the TPTX test, P&G often carried out the Schenk test using different doses on different groups of rats. The lowest dose at which a compound yielded a statistically significant difference in percent trabecular bone with respect to the control group was reported as the LED. (Miller 844.)

86. The Schenk test, unlike the TPTX test, could be used to measure inhibition of mineralization as well as inhibition of bone resorption. (Lenz 133-134)

87. Both the Schenk and TPTX tests were performed in rats, not humans. The results for these tests can sometimes be used to show relative efficacies with respect to compounds which were highly dissimilar. However, as Dr. Benedict testified, it is inappropriate to assume that the results of the Schenk and TPTX tests for 2-pyr EHDP and 3-pyr EHDP can be used to determine what their relative efficacy would be in a human being dosed orally. (Benedict 527.)

88. For all of its tests of activity and toxicity, P&G reported the doses in "mg P/kg." The "mg P" number refers to the number of milligrams of phosphorus actually in the dose. Thus, for risedronate and 2-pyr EHDP, a 1.0 mg P/kg dose corresponds to

about five milligrams of the compound per kilogram of body weight of the test animal. (Miller 913.)

89. In 1985 the standard P&G TPTX test tested at 0.01, 0.1 and 1.0 mg P/kg. (DTX29.)

90. In 1985 P&G submitted a sample of 2-pyr EHDP for testing for potency using the TPTX test at the University of Arizona. The test was carried out at 1.0, 0.1 0.01, and 0.001 mg P/kg. The compound was active at the lowest level tested, 0.001 mg P/kg. (DTX313.)

91. In 1985 P&G submitted a sample of risedronate for testing for potency using the TPTX method at the University of Arizona. The test was carried out at 1.0, 0.1 and 0.01 mg P/kg. The compound was active at the lowest level tested. (PTX139.)

92. In September 1985, P&G tested risedronate using the TPTX method at P&G's facilities. The test was carried out at dosage strengths of 0.1 mg P/kg, 0.01 mg P/kg, 0.001 mg P/kg and 0.0003 mg P/kg. (PTX514.) The compound was active at all doses. (PTX22.)

93. In March, 1985, P&G tested 2-pyr EHDP using the TPTX method at P&G's facilities. The test was carried out at dosage strengths of 1.0, 0.1, 0.01 and 0.001 mg P/kg. The compound was active at all doses. (PTX516.) However, P&G did not test 2-pyr EHDP at 0.0003 mg P/kg, the lowest dose at which it had tested risedronate. It is therefore not possible to determine whether the 2-pyr EHDP is more potent, less potent or has the same potency as risedronate in that test. (Lenz 136-37; McOsker 757-58.)

94. In May 1985, P&G tested 2-pyr EHDP using the Schenk model using the histological method of analysis. The test was performed at doses of 10.0, 1.0, 0.1, 0.01,

0.001 and .0001 mg P/kg. The compound was active at 0.001 mgP/kg. (PTX518.) 2-pyr EHDP was not found active using the histological method of analysis at 0.0001 mg P/kg, and was not tested at the three times higher dose of 0.0003 mg P/kg. (PTX518 at PG191446.)

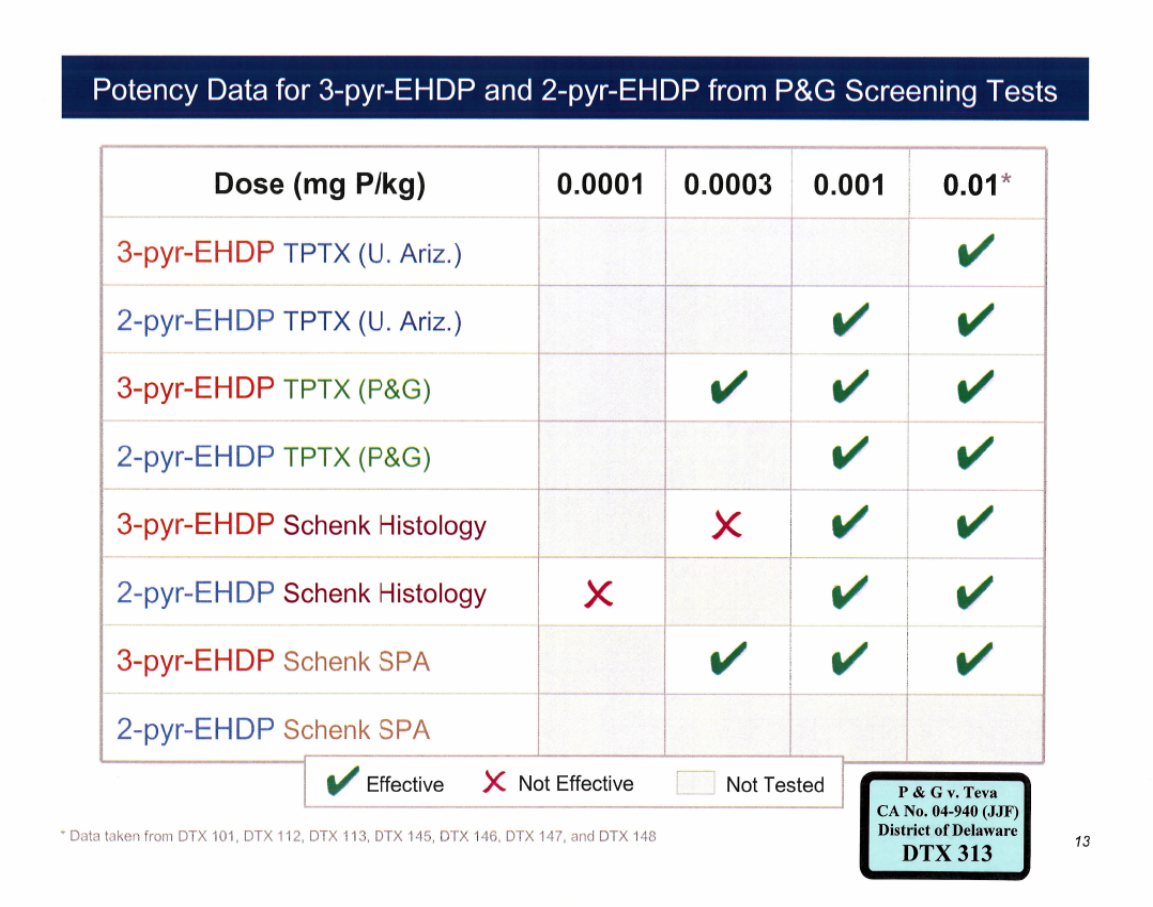
95. In August 1986, P&G tested risedronate using the Schenk model using the histological method of analysis. The test was performed at doses of 1.0 mg P/kg, 0.01 mg P/kg, 0.001 mg P/kg and 0.0003 mg P/kg. At the time, P&G scientists reported that the test results showed that the compound was active at all doses except 0.0003 mg P/kg. At that dose the parameter used to measure activity (percent trabecular bone compared to control) was not statistically significantly different from zero. (PTX22 at PG23097, PG23101; PTX519; Miller 882-83.)

96. Since the 2-pyr EHDP was not tested at 0.0003 mg P/kg, and risedronate was not tested at 0.0001 mg P/kg it is not possible to determine whether 2-pyr EHDP is more potent, less potent or has the same potency as risedronate in the Schenk test using the histological method of analysis. (Lenz 137-38; Miller 909-11; McOsker 757-58.)

97. In August of 1985, P&G also tested risedronate using a different method of analysis, called "single photon absortiometery" or "SPA." This method was generally more sensitive than the histological method, in that it would indicate bone resorption inhibition activity for a test compound at a lower dose than would be determined by the histological method. (PTX22 at PG23097-98.) Using this more sensitive method, P&G concluded that risedronate was active at 0.0003 mg P/kg. However, P&G never tested 2-pyr EHDP using the SPA method, so that it is not possible to determine whether that

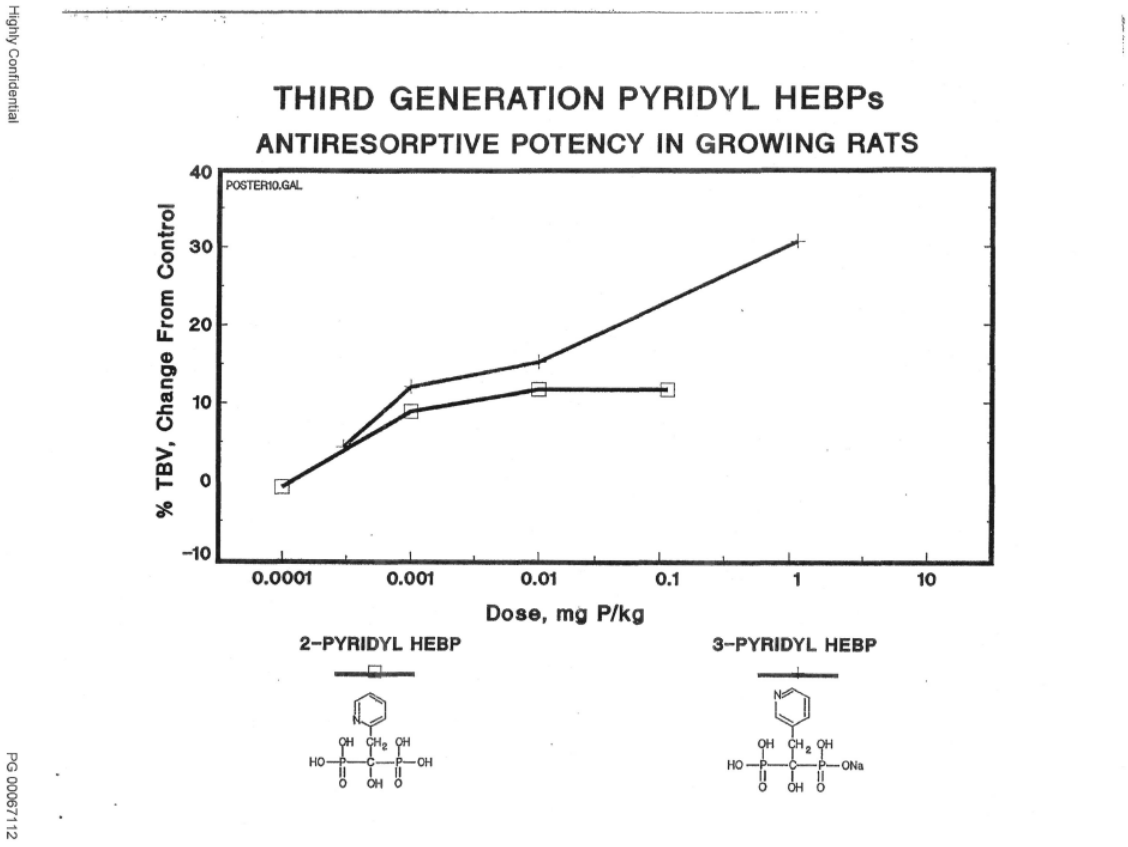
method would have shown the 2-pyr EHDP was more potent, less potent or exhibited equivalent potency compared to risedronate. (McOsker 754.)

98. P&G's activity screening tests of 2-pyr EHDP and risedronate (3-pyr EHDP) are summarized in the chart below. This data shows that no test was ever conducted at P&G from which any conclusion can be drawn as to which compound had the lowest LED. (Lenz 139.)



99. In 1988, P&G scientists submitted a manuscript for publication (DTX144), which included data from the Schenk histological analysis for 2-pyr EHDP and risedronate. The data for each dosage strength were obtained by subtracting the percent trabecular bone for each dose from the control for the experiment. (Lenz 141.) Thus, the data show not only whether the compound was active at the particular dose, but

also quantify that activity. The plotted data, as drawn by P&G's scientists at the time, show that at low doses, 2-pyr EHDP and risedronate are indistinguishable from each other in terms of activity. (Lenz 142-43; DTX144 at PG67112.) The published version of the article does not include the graphical presentation, but does include the same data in tabular form. (DTX74; Miller 945.) The figure as plotted by P&G scientists and submitted for publication in 1988 is shown below.



DTX144.

100. At trial, P&G's litigation expert, Dr. Miller, recalculated the Schenk histological data for 2-pyr EHDP and risedronate differently from the manner in which P&G had done so before this litigation. This recalculation makes the differences between 2-pyr EHDP and risedronate appear larger than they do in P&G's pre-litigation

presentation of the data. (Miller 875-77.) Dr. Miller did not provide a cogent explanation for not using the pre-litigation methods that P&G used both internally and which it published in the scientific literature. (Miller 875-82.)

101. Even using Dr. Miller's methodology, however, there is no significant difference in activity between the two compounds at any therapeutically relevant dose. In particular, the daily therapeutic oral dose of risedronate of five milligrams corresponds to 0.000125 mg P/kg for a 60 kg (132 lb) human patient (Lenz 143-44; Miller 911-14), and at that level, the activity of the two compounds cannot be distinguished from each other, even when the data are presented as Dr. Miller did. (Miller 916; Lenz 144-45.)

102. In the experiments that yielded the data on which Dr. Miller relied, 2-pyr EHDP activity was measured at 0.1 mg P/kg, 0.01 mg P/kg and 0.001 mg P/kg. Risedronate activity was measured at 1.0 mg P/kg, 0.01 mg P/kg, 0.001 mg P/kg and 0.0003 mg P/kg. Thus, the only dosage strengths at which both were measured were 0.01 mg P/kg and 0.001 mg P/kg. The laboratory records, however, show that for the risedronate the test animals mistakenly received a 100-fold excess dose during the 0.01 mg P/kg experiment, which biased that experiment. (PTX519 at PG191472; Miller 897-99.) Accordingly, there is only a single data point, 0.001 mg P/kg, at which a comparison of any sort can be made, and at this point the difference according to P&G's method of comparison was small. (DTX74 at 396, Table VI (12.1 percent for risedronate, 8.9 percent for 2-pyr EHDP).)

103. In 1998, several scientists, including P&G internal expert Dr. Ebetino, published a paper in *Bone*, a refereed journal of which Dr. Miller, one of P&G's experts, is an editor. (DTX36.) In that paper, they reported on bisphosphonate bone resorption

inhibition activity for several compounds, including 2-pyr EHDP and risedronate. The test they used, however, was different from both the Schenk test and the TPTX test. In this test, 2-pyr EHDP was almost three times as active as risedronate. (Lenz 148; DTX36 at 440.) In discussing these results, the authors concluded that the potency of 2-pyr EHDP was essentially equivalent to that of risedronate:

> Replacement of the nitrogen functionality in a different position in the ring structure ([2-pyr EHDP]). . . did not alter the potency of these compounds relative to risedronate.

(Lenz 148; DTX36 at 441.)

104. Example I in the '122 patent sets out an oral dosing regimen for treating osteoporosis using a specific pharmaceutical composition. It states that "[s]imilar results are obtained when" the named bisphosphonate "is replaced with" a compound from a list of 15 bisphosphonates that includes both 2-pyr EHDP and 3-pyr EHDP. (JTX1, col.9, ll.35-65.)

105. Example II in the '122 patent sets out an oral dosing regimen for treating osteoporosis using a specific pharmaceutical composition. It states that "[s]imilar results are obtained when" the named bisphosphonate "is replaced with" a compound from a list of 15 bisphosphonates that includes both 2-pyr EHDP and 3-pyr EHDP. (JTX1, col.10, ll.1-30.)

106. Example III in the '122 patent sets out an injectable dosing regimen for treating hypercalcemia of malignancy using a specific pharmaceutical composition. It states that "[s]imilar results are obtained when" the named bisphosphonate "is replaced with" a compound from a list of 15 bisphosphonates, which includes both 2-pyr EHDP and 3-pyr EHDP. (JTX1, col.10, ll.35-60.)

107. Example IV in the ’122 patent sets out an injectable dosing regimen for treating hypercalcemia of malignancy using a specific pharmaceutical composition. It states that “[s]imilar results are obtained when” the named bisphosphonate “is replaced with” a compound from a list of 15 bisphosphonates, which includes both 2-pyr EHDP and 3-pyr EHDP. (JTX1, col.16, l.55 – col.17, l.15.)

108. To summarize the activity data, in the TPTX test, there is no evidence that risedronate is any more or less active than 2-pyr EHDP. For the Schenk test, the evidence shows that the difference, if any, is slight and not meaningful at therapeutic levels. For the 1998 test, P&G’s own data, published in a refereed journal, indicate that 2-pyr EHDP is actually more active than risedronate by a factor of three. The Court therefore finds that there exists no significant difference in potency between 2-pyr EHDP and risedronate.

2. P&G’s Toxicity Testing Shows That Risedronate Does Not Exhibit Any Unexpected Toxicity Advantage Over 2-pyr EHDP

109. In connection with its work on bisphosphonate compounds, P&G developed a toxicity screening test. For each compound, a group of test animals was administered the test compound at 0.25 mg P/kg, another group at 0.75 mg P/kg and a third group at 2.5 mg P/kg. (DTX109.) Each dose was administered twice, on consecutive days. The animals were then killed and autopsied, and visual analyses were made of internal organs, as well as chemical analyses of certain blood parameters. From this screen, P&G recorded a “no observable effects level” or “NOEL,” which is the highest dose at which no toxic effects were observed. (Eastman 774-75.)

110. For 2-pyr EHDP, P&G observed no toxic effects at 0.25 mg P/kg, but saw evidence of toxicity at 0.75 mg P/kg. P&G therefore assigned to 2-pyr EHDP a NOEL of 0.25 mg P/kg. For risedronate, P&G observed no toxicity at 0.25 mg P/kg or 0.75 mg P/kg, but saw toxic effects at 2.5 mg P/kg. P&G therefore assigned to risedronate an NOEL of 0.75 mg P/kg. (DTX109 at PG66839.)

111. Although the NOEL for risedronate was three times that of 2-pyr EHDP, this fact does not imply that the former is three times less toxic than the latter. P&G scientists recognized that the two-day screen is not appropriate to determine relative toxicity. It is only useful to "predict unacceptably toxic drugs; to determine a valid relative ranking, chronic oral dosing studies would have to be initiated." (DTX114, PG76987.) P&G never conducted such dosing studies for 2-pyr EHDP.

112. In addition, since P&G did not conduct a two-day toxicology screen for 2-pyr EHDP at any dose between 0.25 and 0.75 mg P/kg, the actual NOEL cannot be determined. It could be, for example, that the true NOELs for these compounds are very similar: for 2-pyr EHDP, only slightly below 0.75 mg P/kg and for risedronate, only slightly above it. (Lenz 124-25.)

113. P&G's toxicity expert, Dr. Eastman, recognized the imprecise nature of the two-day i.v. toxicology screen, and characterized the toxicities of 2-pyr EHDP and risedronate (0.25 mg P/kg and 0.75 mg P/kg) as "similar." (DTX84.)

114. In addition to the two-day toxicology screen, P&G carried out another test to screen for liver toxicity. The issue of liver toxicity was important at P&G, since liver toxicity issues were the reason that a prior compound under development was abandoned. (Eastman 811-12.) In that test, 2-pyr EHDP was less toxic than risedronate: the NOEL

for 2-pyr EHDP was twice that of risedronate. (DTX94 at PG10755 and PG10756; Miller 925-26.)

115. One way of considering toxicity is to calculate a therapeutic ratio, or safety ratio, which is defined as a toxic level divided by an effective dose. (Miller 903; Eastman 793-94.) Thus, a drug that shows toxicity at a particular dose may still be completely acceptable if it shows efficacy at a much lower dose. (Miller 905-906.)

116. For 2-pyr EHDP and risedronate, the data indicate that both are completely safe at any conceivable therapeutic dose. The therapeutic ratio (taking into account the actual amount of blood in the body) for 2-pyr EHDP, and assuming a therapeutic dose of 5 mg, is about 13,000. At the time the FDA was seeking ratios of only about 100. Both 2-pyr EHDP and risedronate are "very, very safe drugs," so that any difference between them has no practical significance. (Lenz 129.)

117. Data in Tables II and III of the '406 patent indicate that in the Schenk test, 2-pyr EHDP was "lethally toxic" a dose of 1.0 mg P/kg, but was effective at 0.001 mg P/kg. (JTX1, col.12, l.60 – col.13, l.39.) A therapeutic ratio defined by the lethal dose divided by the lowest effective dose is 1,000, based on the Schenk test. In that same test, alendronate was lethally toxic at a dose of 10 mg P/kg, but was effective only at 0.1 mg P/kg, which yields a therapeutic ratio of only 100, a factor of ten less favorable than for 2-pyr EHDP. Alendronate is an outstanding drug. (Bilezikian 406.) It is approved as "safe and effective" for treatment of bone disease. P&G's expert Dr. Bilezikian prescribes it for osteoporosis patients. (Bilezikian 383-84.) Risedronate (Actonel) exhibits no demonstrated toxicity advantage over alendronate (Fosamax). (Bilezikian 399.) In fact, Fosamax outsells Actonel by two-to-one, even though P&G has spent more

than $1 billion marketing Actonel. (Bilezikian 405; Smith 1013-14.) Since the data in the '406 patent indicate that 2-pyr EHDP has an even more favorable therapeutic ratio than alendronate, there is no basis to conclude that risedronate has any significant safety advantage over 2-pyr EHDP.

118. Finally, the inventor Dr. Benedict admitted that even if 2-pyr EHDP were lethally toxic at 1.0 mg P/kg this would not prevent it from being an effective pharmaceutical product, and that he himself with this information still included it as one of his preferred compounds in December of 1985 when filing the '543 application. (Benedict 501-02.)

119. P&G filed the application for the '122 patent six months after it filed the application for the '406 patent, which contained the data in Table III. Dr. Benedict nevertheless characterized 2-pyr EHDP as a "preferred" compound, along with risedronate. He testified that the toxicity data for 2-pyr EHDP, including P&G's NOEL data and the data in the '406 patent did not imply that the compound would not be suitable as a pharmaceutical. (Benedict 501-02.)

120. One of the goals of bisphosphonate drug development is to find compounds that separate inhibition of bone resorption from inhibition of mineralization. (Bilezikian 375-80.) The data in Tables II and III of the '406 patent show that 2-pyr EHDP inhibits bone resorption at a very low dose (0.001 mg P/Kg), and does not inhibit mineralization at the highest dose tested. (JTX5, col.13, ll.20-39.) This property would have encouraged a person skilled in the art to pursue 2-pyr EHDP and related compounds.

121. P&G's chart of the therapeutic ratios calculated on the basis of NOEL divided by LED (a different basis from the ratio calculated from the data in the '406 patent), even taken at face value, shows that alendronate has a ratio similar to that of 2-pyr EHDP. In fact, both have a therapeutic ratio approximately 100 times more favorable than etidronate, even though etidronate is approved by the FDA as "safe and effective" as a treatment for bone disease. (Miller 906-08.)

122. For the foregoing reasons, the evidence does not support a finding that risedronate has any unexpected toxicity advantage compared to 2-pyr EHDP.

123. P&G has asserted that the difference in therapeutic ratios between 2-pyr EHDP and risedronate is a factor of ten. This assertion is not supported. It is based on an assumption that the LED of risedronate is 0.0003 mg P/kg and that of 2-pyr EHDP is 0.001 mg P/kg. However, 2-pyr EHDP was never tested at the 0.0003 mg P/kg level. Moreover, in a later test, using a different potency screening method, P&G showed that 2-pyr EHDP was more active than risedronate. (DTX36 at 440; Lenz 147-48.) P&G's assertion is also based on an assumption that the NOEL for risedronate is three times higher than that for 2-pyr EHDP. For the reasons discussed above, however, that assumption is also not valid.

F. Claims 4, 16, and 23 of the '122 Patent Would Have Been Obvious in Light of the '406 Patent

1. P&G Failed to Demonstrate a Date of Invention Prior to the Filing Date of the '406 Patent, So That the Entire Patent is Prior Art

124. Dr. James Benedict stated that he had made 3-pyr EHDP (risedronate) in May of 1985. (Benedict 420-21.) However, Dr. Benedict did not testify about the conception of 3-pyr EHDP specifically prior to May of 1985, nor about the conception of

any specific dosing ranges for use with 3-pyr EHDP, nor about any specific dosing ranges of 3-pyr EHDP to treat any diseases.

125. Other than the oral testimony of Dr. Benedict, no other witnesses testified regarding the alleged conception or making of 3-pyr EHDP in May of 1985 by Dr. Benedict or Dr. Perkins. Further, no trial or deposition testimony corroborates Dr. Benedict's oral testimony regarding a May 1985 conception or reduction to practice.

126. Dr. Benedict's testimony is based on his memory of events, which was shown to be unreliable at trial. Dr. Benedict repeatedly testified in detail regarding a conversation in which he received information regarding the first tests on risedronate. He first stated on direct that he received these results from Ms. McOsker in Cincinnati, who came "hustling down the hall, running down the hall." (Benedict 469-70.) On cross-examination he further elaborated that the conversation was not only in Cincinnati, but he identified where in the building, specifically "the back corridor" of the lab as opposed to his office. (Benedict 487.) P&G corrected this testimony through Ms. McOsker who stated that the conversation took place in Norwich, New York. (McOsker 727-28.) She further stated that the conversation in fact took place in Dr. Benedict's office, not in a corridor. (McOsker 761.)

127. At trial, P&G attempted to corroborate Dr. Benedict's testimony by pointing to certain unwitnessed pages from laboratory notebooks. Dr. Benedict testified about pages 15 and 16 (PG53521-22) of a notebook (PTX67) allegedly written in May 1985, and claimed this indicated his first synthesis of 3-pyr EHDP. (Benedict 467.) This notebook was never witnessed by anyone, despite P&G's policy that required that laboratory notebooks be witnessed. (Benedict 504-505.) At the time that this notebook

page was allegedly written, several P&G individuals would have understood the work set forth in the notebook, but none of them witnessed the notebook page. (Benedict 507-09.)

128. Dr. Benedict testified further that the additional discussion on page 16 regarding samples having been sent to Arizona for testing was written at some later point, and there is no indication in the notebook when this occurred. (Benedict 509.) P&G presented no testimony or evidence indicating when, if ever, any samples related to these notebook pages were sent anywhere. Accordingly, this notation does not corroborate any information on this page.

129. Dr. Benedict testified that, when he was done with a notebook, they were sent to a library and microfilmed, but that copies could be obtained later. (Benedict 509-10.)

130. As to this copy of the notebook, PTX67, Dr. Benedict had no information as to where the notebook was stored, or what version was produced (*i.e.*, a copy from microfilm, or a copy that was taken from storage and kept elsewhere at P&G after being microfilmed). (Benedict 510.)

131. Dr. Benedict also testified about pages from a second laboratory notebook, PTX70. His oral testimony was that page 93 (PG54042) also corroborated his testimony regarding conception in May of 1985. Just like the pages in PTX67, this notebook page was not witnessed by anyone. (Benedict 510.) Additionally, it was not even signed by Dr. Benedict. No testimony was provided by any other witnesses regarding this page.

132. As to PTX70, allegedly a copy of the actual notebook, Dr. Benedict testified that the version produced was not the same as that microfilmed and stored by P&G as part of the normal archival system. (Benedict 513-15.) Even as of the time of

trial, Dr. Benedict had not reviewed the entire notebook to determine what changes were made to the notebook since he had sent it for archiving. (Benedict 515.) Accordingly, PTX70, as produced by P&G was not kept in this form as part of the ordinary course of business.

133. No qualified witness, such as a custodian of records of P&G, testified regarding PTX67 or PTX70. No witness stated that PTX67 or PTX70 as offered into evidence is an authentic copy of the original notebook in the form that they were kept as part of the regularly conducted business activities of P&G.

134. P&G provided no testimony from any other witnesses, or any other evidence, that would corroborate, or independently support, Dr. Benedict's claims of conception and reduction to practice of 3-pyr EHDP prior to June 6, 1985. Additionally, neither Dr. Benedicts testimony or these exhibits indicate that Dr. Benedict or Dr. Perkins was in possession of any salts or esters of 3-pyr EHDP, any dosing size for 3-pyr EHDP, or any method of using 3-pyr EHDP with particular dosing sizes, prior to June 6, 1985.

2. The Claimed Inventions of the '122 Patent Would Have Been Obvious in View of the '406 Patent

135. In addition to the claimed invention of claim 15 discussed above, the '406 patent includes additional information about 2-pyr EHDP and eight other bisphosphonate compounds. Those compounds include the known bisphosphonates etidronate ("EHDP"), clodronate ("Cl_2MDP"), pamidronate ("APD"), and alendronate ("ABDP").

136. The '406 patent provides TPTX assay results that show that 2-pyr EHDP is the most potent of the eight compounds in inhibiting bone resorption, and that it is effective at a dose 10 times lower than the lowest dose at which any of the other compounds was found to be effective. (JTX5, col.8, ll.35-53.)

137. The ’406 patent provides Schenk assay results which indicate that 2-pyr EHDP is the most potent of the eight compounds in inhibiting bone resorption. The ’406 patent provides Schenk assay results indicating that 2-pyr EHDP did not cause a statistically significant inhibition of bone mineralization at the highest dose level at which the assay was completed. (JTX5, col.13, ll.20-39.) A Schenk assay measures a compound’s effectiveness in inhibiting bone resorption.

138. For the reasons discussed above as well as in light of the information contained in the ’406 patent specification, the inventions claimed in claims 4, 16 and 23 of the ’122 patent would have been obvious to a person skilled in the art.

G. “Commercial Success” is Factually Inapplicable in This Case

139. Procter & Gamble’s expert, Dr. Smith, did not demonstrate any connection between the patented invention and Procter & Gamble’s sales of Actonel.

140. Teva USA’s expert, Dr. David, is an expert in the field of economics. (David 293.) Dr. David testified that where the prior art was not known in the marketplace, the performance of that product in the commercial marketplace has no significance with respect to the obviousness of a patent claim from an economics point of view. (David 298-99.)

141. Dr. Smith is an expert in marketing, not economics. Dr. Smith provided no testimony regarding the economic significance of the performance of Actonel in the commercial marketplace on the obviousness of the ’122 patent.

142. Actonel was approved by the FDA and launched in 1998. (Statement of Undisputed Facts 15.) Dr. Smith did not analyze the sales or marketing of Actonel for the first two years of its commercial availability (1998 to 2000). (Smith 995.)

143. Actonel is not a blockbuster drug. Dr. Smith stated that that term is generally reserved for a pharmaceutical drug with over $1 billion a year in sales. (Smith 962.) Actonel has never achieved over $1 billion a year in sales, and has actually averaged close to half that amount since the year 2000.

144. Dr. Smith only analyzed a portion of the marketing materials for Actonel. He did not analyze any of the television, radio, or internet advertisements for Actonel. (Smith 996.)

145. Since 2000 Procter & Gamble has spent over $1 billion in marketing. (Smith 1013.) This figure does not include any expenses from prior to 2000. Accordingly, Procter & Gamble has spent over $1 billion to achieve close to $2.7 billion in sales. Therefore, a significant portion of the sales of Actonel were due to marketing, and not to the patented features of the product.

146. Despite being on the market since 1998, Actonel has only achieved a market share of 25 percent. (Smith 968.) The dominant bisphosphonate product in the market is Merck's Fosamax product.

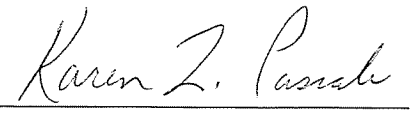
147. Dr. Smith provided no testimony with respect to how 2-pyr EHDP would have sold had it been marketed by Procter & Gamble or any other company.

148. Accordingly, the Court finds that, to the extent pertinent to this case, P&G has not established that there is any commercial success in this case attributable to the inventions of the asserted claims.

Respectfully submitted,

YOUNG CONAWAY STARGATT
& TAYLOR, LLP

December 20, 2006

By 

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CERTIFICATE OF SERVICE

I, Karen L. Pascale, Esquire, hereby certify that on December 20, 2006, I caused to be electronically filed a true and correct copy of the foregoing document with the Clerk of the Court using CM/ECF, which will send notification that such filing is available for viewing and downloading to the following counsel of record:

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